ALKYLAMINOALKYL-TERMINATED SULFIDE/SULFONYL-CONTAINING PROPARGYL AMINO-DIOL COMPOUNDS FOR TREATMENT OF HYPERTENSION

FIELD OF THE INVENTION

Renin-inhibiting compounds are known for control of hypertension. Of particular interest herein are compounds useful as renin inhibiting agents.

BACKGROUND OF THE INVENTION

Renin is a proteolytic enzyme produced and secreted into the bloodstream by the juxtaglomerular cells of the kidney. In the bloodstream, renin cleaves a peptide bond in the serum protein angiotensinogen to produce a decapeptide known as angiotensin I. A second enzyme known as angiotensin converting enzyme, cleaves angiotensin I to produce the octapeptide known as angiotensin II. Angiotensin II is a potent pressor agent responsible for vasoconstriction and elevation of cardiovascular pressure. Attempts have been made to control hypertension by blocking the action of renin or by blocking the formation of angiotensin II in the body with inhibitors of angiotensin I converting enzyme.

Classes of compounds published as inhibitors of the action of renin on angiotensinogen include renin antibodies, pepstatin and its analogs, phospholipids, angiotensinogen analogs, pro-renin related analogs and peptide aldehydes.

A peptide isolated from actinomyces has been reported as an inhibitor of aspartyl proteases such as pepsin, cathepsin D and renin [Umezawa et al, in J. Antibiot. (Tokyo), 23, 259-262 (1970)]. This peptide,

known as pepstatin, was found to reduce blood pressure in vivo after the injection of hog renin into nephrectomized rats [Gross et al, Science, 175, 656 (1971)]. Pepstatin has the disadvantages of low solubility and of inhibiting acid proteases in addition to renin. Modified pepstatins have been synthesized in an attempt to increase the specificity for human renin over other physiologically important enzymes. While some degree of specificity has been achieved, this approach has led to rather high molecular weight hepta- and octapeptides [Boger et al, Nature, 303, 81 (1983)]. High molecular weight peptides are generally considered undesirable as drugs because gastrointestinal absorption is impaired and plasma stability is compromised.

Short peptide aldehydes have been reported as renin inhibitors [Kokubu et al, Biochim. Biophys. Res. Commun., 118, 929 (1984); Castro et al, FEBS Lett., 167, 273 (1984)]. Such compounds have a reactive C-terminal aldehyde group and would likely be unstable in vivo.

Other peptidyl compounds have been described as renin inhibitors. EP Appl. #128,762, published 18 December 1984, describes dipeptide and tripeptide glyco-containing compounds as renin inhibitors [also see Hanson et al, Biochm. Biophys. Res. Comm., 132, 155-161 (1985), 146, 959-963 (1987)]. EP Appl. #181,110, published 14 May 1986, describes dipeptide histidine derivatives as renin inhibitors. EP Appl. #186,977 published 9 July 1986 describes renin-inhibiting compounds containing an alkynyl moiety, specifically a propargyl glycine moiety, attached to the main chain between the N-terminus and the C-terminus, such as N-[4(S)-[(N)-[bis(1-naphthylmethyl)acetyl]-DL-propargylglycylamino]-3(S)-hydroxy-6-methylheptanoyl]-L-isoleucinol. EP Appl. #189,203, published 30 July 1986, describes peptidyl-aminodiols as renin inhibitors. EP Appl. #200,406,

published 10 December 1986, describes alkylnaphthylmethylpropionyl-histidyl aminohydroxy alkanoates as renin inhibitors. EP Appl. #216,539, published 1 April 1987, describes alkylnaphthylmethylpropionyl aminoacyl aminoalkanoate compounds as renin inhibitors orally administered for treatment of renin-associated hypertension. PCT Application No. WO 87/04349, published 30 July 1987, describes aminocarbonyl aminoacyl hydroxyether derivatives having an alkylamino-containing terminal substituent and which are described as having renin-inhibiting activity for use in treating hypertension. EP Appl. #300,189 published 25 January 1989 describes amino acid monohydric derivatives having an alkylamino-alkylamino N-terminus and a β-alanine-histidine or sarcosyl-histidine attached to the main chain between the N-terminus and the C-terminus, which derivatives are mentioned as useful in treating hypertension. U.S. Patent No. 4,902,706 which issued 13 February 1990 describes a series of histidineamide-containing amino alkylaminocarbonyl-H-terminal aminodiol derivatives for use as renin inhibitors. U.S. Patent No. 5,032,577 which issued 16 July 1991 describes a series of histidineamide-aminodiol-containing renin inhibitors.

Several classes of sulfonyl-containing amino-diol renin-inhibitor compounds are known. For example, EP #229,667 published 22 July 1987 describes generally alkylsulfonyl histidineamide amino diol C-terminated-alkyl compounds as renin inhibitors. Australian Patent Application #30797/89 published 7 September 1989 describes alkylsulfonyl histineamide amino diol C-terminated-alkyl compounds as renin inhibitors, such as (S)-α-[(S)-α-[(t-butyl-sulphonyl)methyl]hydrocinnamamido]-N-[(1S,2R,3RS)-1-(cyclohexylmethyl)-2,3-dihydroxy-4,4-dimethylpentyl]-imidazole-4-propionamide and (S)-α-[(S)-α-[(t-

butylsulphonyl)methyl]hydrocinnamamido]-N-[(1S,2R,3S,4RS)-1-(cyclohexylmethyl)-2,3-dihydroxy-4-methylhexyl]imidazole-4-propionamide. U.S. Patent No. 4,914,129 issued 3 April 1990 describes sulfone-containing amino-hydroxyvaleryl compounds for use as antihypertensive agents, such as the compounds N-[2(S)-benzyl-3-tert-methylsulfonylpropionyl]-His-Cha-Val-n-butylamide and N-[2(R)-benzyl-3-tert-methylsulfonylpropionyl]-His-Cha-Val-n-butylamide. EP #416,373 published 13 March 91 describes alkylsulfonyl histidineamide amino diol compounds as renin-inhibitors, such as (S)-α-[(S)-α-[(tert-butylsulfonyl)methyl]-hydrocinnamamido]-N-[(1S,2R,3S)-1-(cyclohexylmethyl)-3-cyclopropyl-2,3-dihydroxypropyl]-imidazol-4-propionamide and (S)-α-[(S)-α-[(tert-butylsulfonyl)methyl]-hydrocinnamamido]-N-[(1S,2R,3R/S)-1-(cyclohexylmethyl)-3-cyclopropyl-2,3-dihydroxybutyl]imidazol-4-propionamide.

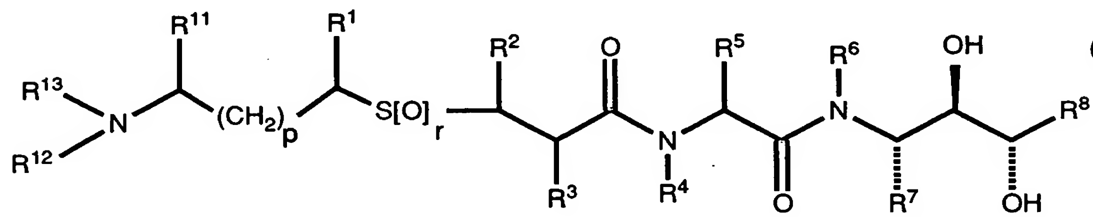
Alkylaminoalkyl-terminated amino-diol renin-inhibitor compounds are known. For example, U.S. Patent No. 4,900,745 which issued 13 February 1990 describes poly(aminoalkyl)aminocarbonyl amino-diol amino acid derivatives as antihypertensive agents such as O-{N-[2-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino}-ethyl]-N-methylaminocarbonyl}-3-L-homophenyllactyl-α-(R)-ethyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane and O-{N-[2-{N-[2-(N,N-dimethylamino)ethyl]-N-methylamino}-ethyl]-N-methylaminocarbonyl}-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane. U.S. Patent No. 4,902,706 which issued 20 February 1990 describes aminoalkylaminocarbonyl amino-diol amino acid derivatives as antihypertensive agents such as O-{N-[2-(N,N-dimethylamino)ethyl]-N-methylaminocarbonyl}-3-L-homophenyllactyl-α-(R)-ethyl-β-alanineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane and O-{N-[2-(N,N-

dimethylamino)ethyl]-N-methylaminocarbonyl-3-L-phenyllactyl-L-leucineamide of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane.

Propargyl-group-containing amino-diol renin inhibitors are known. For example, U.S. Patent No. 5,227,401 which issued 13 July 1993 describes a series of ethynyl alanine amino diol compounds as renin inhibitors for treatment of hypertension including, specifically, the compound N1-[1R*-[[[1S,1R*-(cyclohexylmethyl)-2S*,3R*-dihydroxy-5-methylhexyl] amino]carbonyl]-3-butynyl-N4-[2-dimethyl-amino)ethyl]-N-4-methyl-2S*-(phenylmethyl)butanediamide.

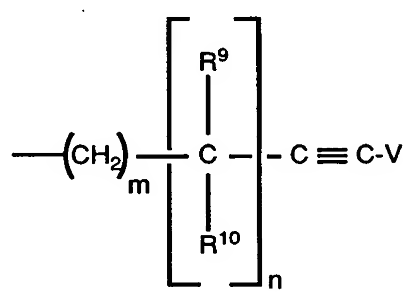
DESCRIPTION OF THE INVENTION

Alkylaminoalkyl-terminated sulfide-sulfonyl-containing propargyl amino diol compounds, having utility as renin inhibitors for treatment of hypertension in a subject, constitute a family of compounds of general Formula I:



(I)

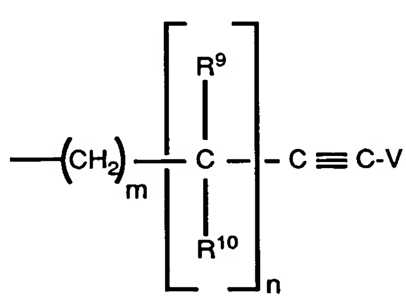
wherein each of R^1 and R^{11} is a group independently selected from hydrido, alkyl, alkylaminoalkyl and phenyl; wherein p is a number selected from zero through five, inclusive; wherein r is a number selected from zero, one and two; wherein R^2 is selected from hydrido and alkyl; wherein R^3 is a group selected from hydrido, cycloalkylalkyl, aralkyl and haloaralkyl; wherein each of R^4 and R^6 is a group independently selected from hydrido and methyl; wherein R^5 is a propargyl moiety or a propargyl-containing moiety selected from



wherein V is selected from hydrido, alkyl, cycloalkyl, aryl and aralkyl; wherein each of R^9 and R^{10} is a group independently selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl and aryl; wherein m is a number

selected from zero through three; wherein n is a number selected from zero through three; wherein R^7 is a group selected from alkyl, cycloalkylalkyl and aralkyl; wherein R^8 is a group selected from hydrido, alkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, alkenyl and haloalkenyl; wherein each of R^{12} and R^{13} is a group independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkylacyl, aryl, aralkyl, haloaryl and haloaralkyl; and wherein any one of said R^1 through R^{13} groups having a substitutable position may be substituted with one or more groups selected from alkyl, hydroxy, hydroxyalkyl, halo, alkoxy, alkoxyalkyl and alkenyl; or a pharmaceutically-acceptable salt thereof.

A preferred family of compounds consists of compounds of Formula I wherein each of R^1 and R^{11} is independently selected from hydrido, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, N,N-dimethylaminomethyl, N,N-diethylaminomethyl, N,N-diethylaminoethyl and phenyl; wherein p is a number selected from zero through four, inclusive; wherein r is a number selected from zero, one and two; wherein R^2 is selected from hydrido and alkyl; wherein R^3 is selected from hydrido, cycloalkylalkyl, phenylalkyl, halophenylalkyl, naphthylalkyl and halonaphthylalkyl; wherein each of R^4 and R^6 is independently selected from hydrido and methyl; wherein R^5 is a propargyl moiety or a propargyl-containing moiety selected from



wherein V is selected from hydrido, alkyl, phenyl and benzyl; wherein each of R^9 and R^{10} is independently selected from hydrido, alkyl, alkenyl, alkynyl, cycloalkyl and aryl; wherein m is a number selected from zero through three; wherein n is a number selected from zero through three; wherein R^7 is selected from cyclohexylmethyl and benzyl, either one of which may be substituted with one or more groups selected from alkyl, hydroxy and alkoxy; wherein R^8 is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkenyl and haloalkenyl; and wherein each of R^{12} and R^{13} is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkanoyl, halophenyl, phenylalkyl, halophenylalkyl, naphthyl, halonaphthyl, naphthylalkyl and halonaphthylalkyl; or a pharmaceutically-acceptable salt thereof.

A more preferred family of compounds consists of compounds of Formula I wherein each of R^1 and R^{11} is independently selected from hydrido, methyl, ethyl, n-propyl and isopropyl; wherein p is a number selected from zero through three, inclusive; wherein r is a number selected from zero, one and two; wherein R^2 is selected from hydrido, methyl, ethyl and n-propyl; wherein R^3 is selected from hydrido, cyclohexylmethyl, benzyl, phenylethyl, fluorobenzyl, fluorophenylethyl, chlorobenzyl, chlorophenylethyl, naphthylmethyl, naphthylethyl, fluoronaphthylmethyl and chloronaphthylmethyl; wherein each of R^4 and R^6 is independently selected from hydrido and methyl; wherein R^5 is is selected from

$$-(CH_2)_m-C\equiv C\text{-}V$$

wherein V is selected from hydrido and alkyl; wherein m is a number selected from one through three; wherein R^7 is cyclohexylmethyl; wherein R^8 is selected from methyl,

ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopropylmethyl, cyclobutylmethyl, cyclohexylmethyl, allyl and vinyl; and wherein each of R^{12} and R^{13} is independently selected from hydrido, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclopropylmethyl, cyclopropylethyl, propylcarbonyl, ethylcarbonyl, methylcarbonyl, phenyl, benzyl, phenylethyl, monochlorophenyl, dichlorophenyl, monofluorophenyl, difluorophenyl, monochlorophenylmethyl, monochlorophenylethyl, dichlorophenylmethyl, dichlorophenylethyl, naphthyl, monofluoronaphthyl, monochloronaphthyl, naphthylmethyl, naphthylethyl, fluoronapthylmethyl and chloronaphthylethyl; or a pharmaceutically-acceptable salt thereof.

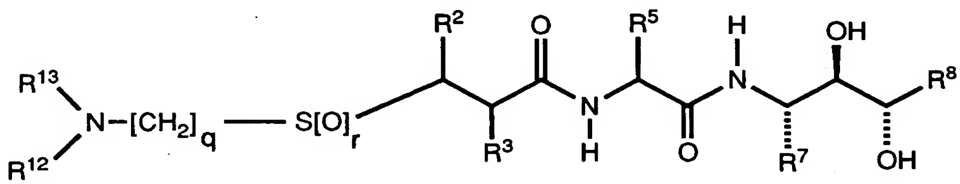
An even more preferred family of compounds consists of compounds Formula I wherein each of R^1 and R^{11} is independently hydrido or methyl; wherein p is a number selected from zero through three, inclusive; wherein r is zero or two; wherein R^2 is selected from hydrido, methyl, ethyl and n-propyl; wherein R^3 is selected from hydrido, cyclohexylmethyl, benzyl, phenylethyl, phenylpropyl, fluorobenzyl, fluorophenylethyl, chlorobenzyl, chlorophenylethyl, naphthylmethyl, naphthylethyl, fluoronaphthylmethyl and chloronaphthylmethyl; wherein each of R^4 and R^6 is hydrido; wherein R^5 is selected from cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl and cyclohexylpropyl; wherein R^7 is cyclohexylmethyl; wherein R^8 is selected from

$$-(CH_2)_m-C\equiv C\text{-}V$$

wherein V is selected from hydrido and alkyl; wherein m is one or two; wherein each of R^9 and R^{10} is independently

selected from hydrido, methyl, ethyl, n-propyl, isopropyl, cyclopropylmethyl, phenyl, benzyl, monochlorophenyl and dichlorophenyl; or a pharmaceutically-acceptable salt thereof.

A highly preferred family of compounds consists of compounds of Formula II:



(II)

wherein q is two or three; wherein r is zero or two; wherein R^2 is selected from hydrido, methyl, ethyl and phenyl; wherein R^3 is selected from hydrido, cyclohexylmethyl, benzyl, fluorobenzyl, chlorobenzyl, fluoronaphthylmethyl and chloronaphthylmethyl; wherein each of R^4 and R^6 is hydrido; wherein R^5 is selected from

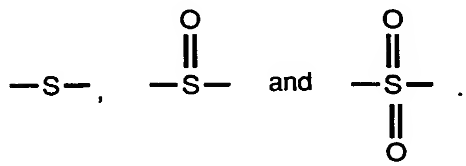
$$-(CH_2)_m-C\equiv C\text{-}V$$

wherein V is selected from hydrido and methyl; wherein m is one or two; wherein R^7 is cyclohexylmethyl; wherein R^8 is selected from n-propyl, isobutyl, cyclopropyl, cyclopropylmethyl, allyl and vinyl; wherein each of R^{12} and R^{13} is independently selected from methyl, ethyl and isopropyl; or a pharmaceutically-acceptable salt thereof.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido group may be attached, for example, to an oxygen atom to form a hydroxyl group; or, as another example, one hydrido group may be attached to a carbon atom to form a $>CH-$ group; or, as another example, two hydrido groups may be attached to a carbon

atom to form a $-CH_2-$ group. Where the term "alkyl" is used, either alone or within other terms such as "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms. The term "cycloalkyl" embraces cyclic radicals having three to about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The terms "alkylol" and "hydroxyalkyl" embrace linear or branched alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably three to about ten carbon atoms, and containing at least one carbon-carbon double bond, which carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety. The term "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about ten carbon atoms, and containing at least one carbon-carbon triple bond. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy group. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy groups attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl groups. Preferred aryl groups are those consisting of one, two, or three benzene rings. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl and biphenyl. The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, phenylbutyl, diphenylethyl and napthylmethyl. The terms

"benzyl" and "phenylmethyl" are interchangeable. Each of the terms sulfide, sulfinyl, and "sulfonyl", whether used alone or linked to other terms, denotes, respectively, the divalent radicals



The term "alkenylalkyl" denotes a radical having a double-bond unsaturation site between two carbons, and which radical may consist of only two carbons or may be further substituted with alkyl groups which may optionally contain additional double-bond unsaturation. For any of the foregoing defined radicals, preferred radicals are those containing from one to about fifteen carbon atoms.

Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, methylbutyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a plurality of unsaturated bonds, with such plurality of bonds either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

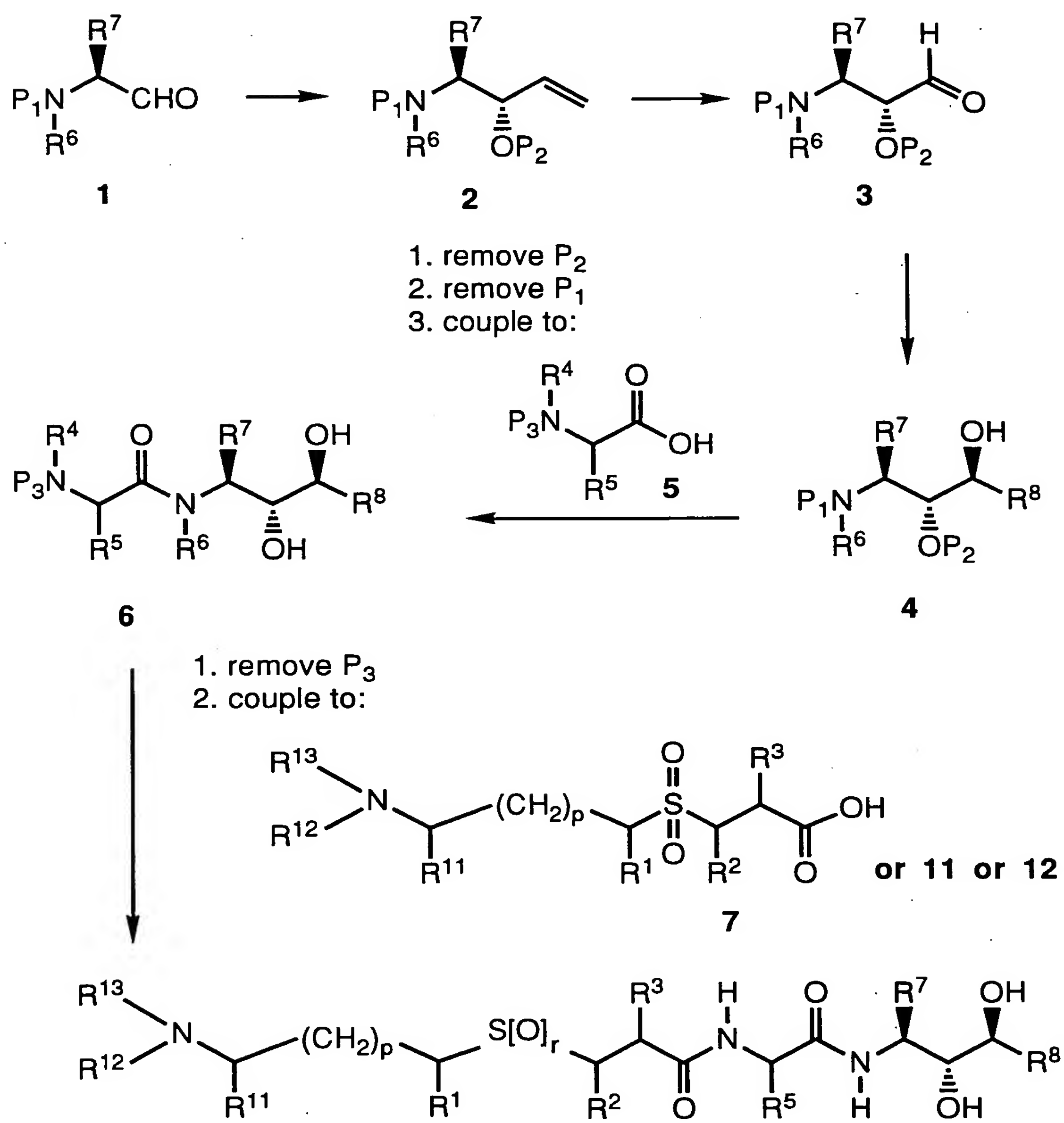
Also included in the family of compounds of Formula I are isomeric forms, including diastereoisomers.

Compounds of Formula I would be useful to treat various circulatory-related disorders. As used herein, the term "circulatory-related" disorder is intended to embrace cardiovascular disorders and disorders of the circulatory system, as well as disorders related to the circulatory system such as ophthalmic disorders, including glaucoma. In particular, compounds of Formula

I would be useful to inhibit enzymatic conversion of angiotensinogen to angiotensin I. When administered orally, a compound of Formula I would be expected to inhibit plasma renin activity and, consequently, lower blood pressure in a patient such as a mammalian subject (e.g., a human subject). Thus, compounds of Formula I would be therapeutically useful in methods for treating hypertension by administering to a hypertensive subject a therapeutically-effective amount of a compound of Formula I. The phrase "hypertensive subject" means, in this context, a subject suffering from or afflicted with the effects of hypertension or susceptible to a hypertensive condition if not treated to prevent or control such hypertension. Other examples of circulatory-related disorders which could be treated by compounds of the invention include congestive heart failure, renal failure and glaucoma.

Description of the Synthetic Methods for the Preparation of the Renin Inhibitors of the Invention

Synthetic Scheme 1



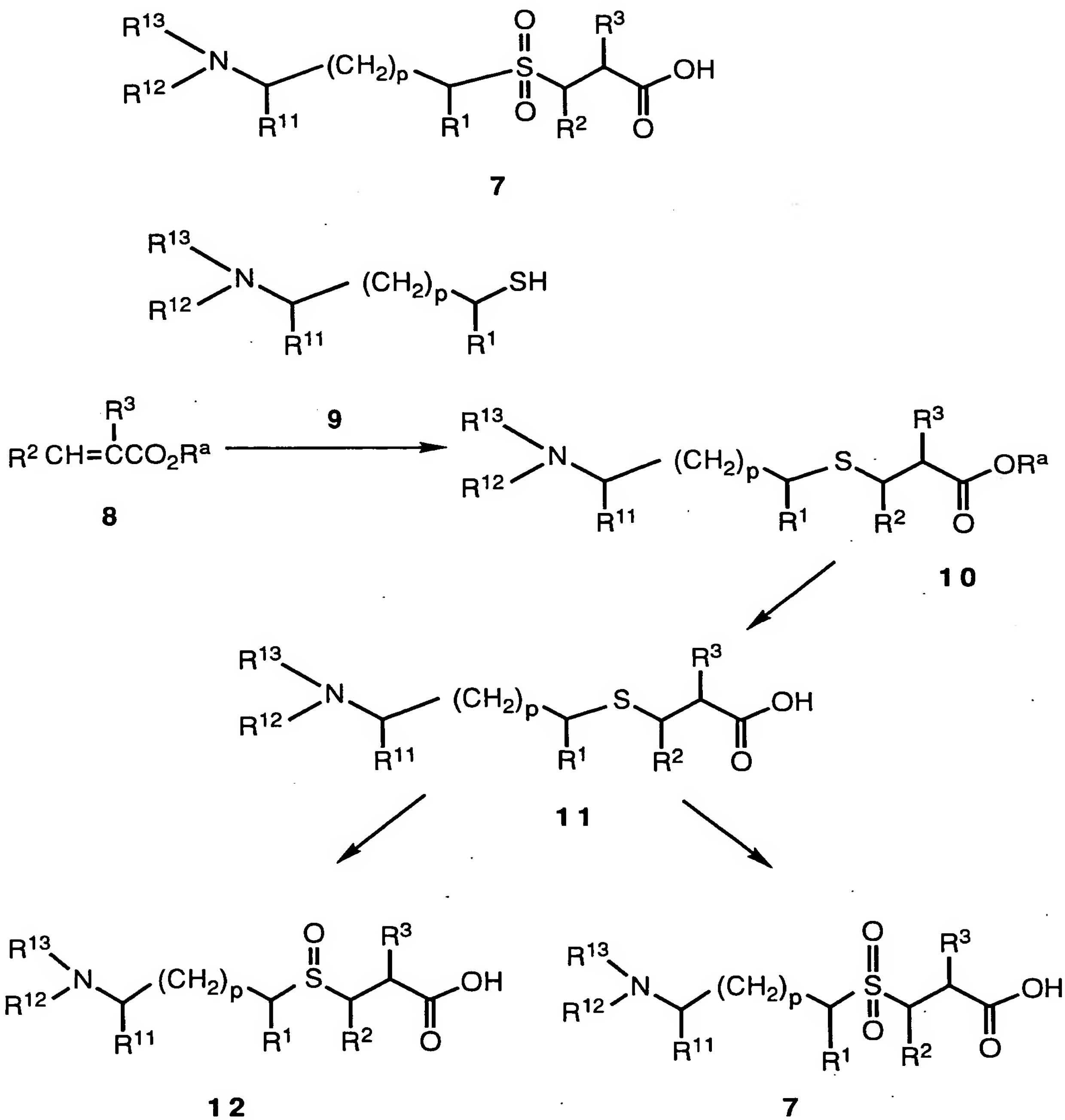
Formula I

wherein R^1 through R^{13}, r and p are as defined above.

A suitably protected amino aldehyde 1 is treated with a Grignard reagent or other organometallic reagent, preferably vinylmagnesium bromide, to obtain the vinyl carbinol 2. This material, suitably protected, is oxidized, preferably with ozone, followed by dimethyl sulfide or zinc treatment, to give intermediate 3. The preceeding process is exemplified in Hanson et al, J. Org. Chem., 50, 5399 (1985). This aldehyde is reacted with an organometallic reagent such as isobutylmagnesium chloride to give intermediate 4. Compound 4 is deprotected then coupled, using standard amide/peptide coupling methodology to protected cycloalkylalkyl-containing amino acid derivatives 5 to give compound 6. These standard coupling procedures such as the carbodiimide, active ester (N-hydroxysuccinimide), and mixed carbonic anhydride methods are shown in Benoiton et al, J. Org. Chem., 48, 2939 (1983) and Bodansky et al, "Peptide Synthesis", Wiley (1976). Cyclopropylmethyl-containing amino acid derivatives may be prepared by cyclopropanation of allylglycine using procedures such as found in Vorbruggen, Tetrahedron Letters, 9, 629 (1975). Intermediate 6 is then deprotected, then coupled to intermediate 7 or 11 or 12 using the standard amide/peptide coupling methodology, to give compounds of Formula I. Suitable protecting groups may be selected from among those reviewed by R. Geiger in "The Peptides", Academic Press, N.Y. vol. 2 (1979). For example, P_1 or P_3 may be Boc or Cbz; P_2 may be a typical oxygen protective group such as acetyl or t-butyldimethylsilyl.

Synthetic Scheme 2

Preparation of 7:



wherein R^1-R^3, R^9-R^{13} and p are as defined above and R^a is lower alkyl or benzyl.

Intermediate 7 may be prepared according to Synthetic Scheme 2. 1,4 addition of a suitable thiol 9 to a suitable acrylic acid benzyl ester 8 in the presence of base catalysts such as triethyl amine or benzyltrimethylammonium hydroxide, afforded α, β disubstituted thio-propionic acid alkyl esters 10. In the case of R^2 = H, a suitable malonic acid dialkyl ester is hydrolyzed to a mono ester, followed by concomitant decarboxylative dehydration to provide α substituted acrylic acid alkyl ester. Compound 10 is converted into its corresponding thio-propionic acid 11 via debenzylation. Compound 11 then is further converted into either its corresponding sulfoxide 12 or sulfone 7 via oxidation with 3-chloroperbenzoic acid or potassium peroxomonosulfate respectively.

Abbreviations: P_1 is an N-protecting group; P_2 is H or an oxygen protecting group; P_3 is an N-protecting group.

The following Steps 1-13 constitute specific exemplification of methods to prepare starting materials and intermediates embraced by the foregoing generic synthetic schemes. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare the compounds of Steps 1-13. All temperatures expressed are in degrees Centigrade. Compounds of Examples 1-13 may be prepared by using the procedures described in the following Steps 1-13:

Step 1: Preparation of (2R,3S)-N-[(tert-Butyloxy)carbonyl]-3-amino-2-acetoxy-4-phenylbutanal

Ozone/oxygen was bubbled at -70°C into a solution of (3S,4S)-N-[(tert-Butyloxy)carbonyl]-4-amino-3-acetoxy-5-phenylpentene (2.55g, 8.0 mmol) [prepared by the method of Hanson et al, J. Org. Chem., 50, 5399 (1985)] in 100mL of methylene chloride until a deep blue color persisted. Oxygen was introduced until the blue color completely faded, then 3.0 mL of Me_2S was added and the solution was allowed to warm to 0-5°C and stand overnight. The solvent was removed at 0°C under vacuum yielding the title compound as a thick yellow oil which was used in the following step without purification.

Step 2: Preparation of (2S,3R,4S)-N-[(tert-Butyloxy)carbonyl]-2-amino-1-phenyl-3,4-dihydroxy-6-methylheptane

The oil prepared in Step 1 was dissolved under nitrogen in 100mL of dry THF and cooled to -70°C. To this solution was added 13mL (26mmol) of a 2.0M solution of isobutylmagnesium chloride in ether and the stirred mixture was allowed to warm to room temperature and stir for 2 hrs. After decomposition with MeOH/H_2O the mixture was diluted with ether, washed with saturated NH_4Cl solution twice, then dried and the solvents stripped off under vacuum. The

residue was allowed to stand overnight in 80% MeOH-H_2O containing excess ammonium hydroxide. The MeOH was stripped off and the mixture was extracted with ether. These extracts were combined, washed with water, dilute $KHSO_4$, then dried and evaporated to give 2.36g of a yellow glass which crystallized from 50mL of pentane on standing overnight. The yellow-white powder obtained was recrystallized from ether-hexane and furnished the title compound (0.41g) as white, hairy needles, mp 134-136°C, Rf (ether): single spot, 0.6. By chromatography of the mother liquors and crystallization of the appropriate fractions, an additional 0.22g of product, mp 138-139°C, was obtained. Anal: Calcd. for $C_{19}H_{31}NO_4$ (337.45): C, 67.62; H, 9.26; N, 4.15. Found: C, 67.51; H, 9.43; N, 4.24.

Step 3: Preparation of (2S,3R,4S)-N-[(tert-Butyloxy)carbonyl]-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The diol of Step 2, 0.27g, was reduced in MeOH with 60psi H_2 at 60°C in 3 hrs using 5% Rh/C catalyst. After filtering, the solvent was stripped off and the white crystals were recrystallized from CH_2Cl_2-hexane to furnish tiny needles of the title compound, 0.19g, mp 126-128°C; further recrystallization gave mp 128.5-129.5°C. Rf (ether): single spot, 0.8. Anal: Calcd. for $C_{19}H_{37}NO_4$ (343.50): C, 66.43; H, 10.86, N, 4.08. Found: C, 66.43; H, 11.01; N, 4.03.

Step 4: Preparation of (2S,3R,4S)-2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The title compound of Step 3 (10g) was dissolved 6.9N HCl in dioxane (300mL). The mixture was stirred for 30 minutes at room temperature. The solvent was removed in vacuo and to the residue was added 5% aqueous sodium hydroxide (30mL) until a pH of 14 was obtained. This mixture was extracted with ether and the ether extract was washed with water and brine, then the solvent was

evaporated to give the title compound (7.3g, 100% yield). ^1H NMR: 300 MHz spectrum consistent with proposed structure. Anal: calcd. for $C_{14}H_{29}NO_2$: C, 69.07; H, 12.01; N, 5.78. Found: C, 69.19; H, 12.34; N, 5.78.

Step 5: L-Boc-*C*-propargylglycine

L-*C*-Propargylglycine (10g) [prepared by the method of Schwyzer et al., Helv. Chim. Acta 59, 2181 (1976)] was suspended in tetrahydrofuran (30mL). Water (30mL), potassium carbonate (36.7g), and di-*tert*-butyl-dicarbonate (21.9g) were added. Additional water was added to produce a solution which was stirred for 12 hours at room temperature. The organic solvent was then evaporated and the aqueous solution was washed with ether, then acidified to pH 3 with 1N aqueous citric acid. The solution was extracted with methylene chloride and the solvent evaporated to give the title compound (18.9g, 97% yield), used without further purification.

Step 6: Preparation of Boc L-*C*-propargylglycine amide of (2S,3R,4S) 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

Boc L-*C*-propargylglycine (1.2g) was dissolved in methylene chloride (5 mL) and N-methyl piperidine (0.57g) was added. The mixture was cooled to zero degrees centigrade and isobutyl chloroformate (0.78g) was added. The mixture was stirred for 10 minutes whereupon the title compound of Step 4 (1.4g) in methylene chloride (5 mL) was added and this mixture stirred for 15 minutes at 0°C and 4°C for 12 hours. The reaction mixture was washed successively with 1N citric acid, saturated sodium hydrogen carbonate, water and brine. The organic layer was dried over magnesium sulfate and evaporated to dryness. The residue was chromatographed on silica gel to give the title compound as a colorless oil. 300 MHz ^1H NMR: consistent with proposed structure.

Step 7: Preparation of L-*C*-propargylglycine amide of (2S,3R,4S) 2-amino-1-cyclohexyl-3,4-dihydroxy-6-methylheptane

The title compound of Step 6 (0.76g) was dissolved in a mixture of trifluoroacetic acid (4.9 mL) and methylene chloride (4.9 mL), and stirred for 30 minutes at room temperature. The solvent was then evaporated and the residue taken up in ethyl acetate. The organic layer was washed with saturated sodium hydrogen carbonate, water and brine, then dried over magnesium sulfate and evaporated to give the title amine. 300 MHz ^1H NMR: consistent with proposed structure.

Step 8: Preparation of ethyl α-methylenebenzenepropanoate

A mixture of of KOH (8.5g) in ethanol (100mL) was added at room temperature to benzylmalonic acid diethyl ester (40g) in ethanol (80mL) and the solution was stirred at room temperature overnight, then concentrated by evaporation. Water (14mL) was added and then the mixture was acidified in an ice bath with concentrated hydrochloric acid (12.6mL). The mixture was partitioned between water and ether; the organic phase was separated, dried and the ether was evaporated. The residue was treated with pyridine (26mL), piperidine (1.22g) and paraformaldehyde (3.56g). The mixture was heated in an oil bath (130°) for 90 minutes, then cooled, and water (440mL) was added. The mixture was extracted 3 times with n-hexane (150mL). The combined organic phases were washed successively with water, 1N HCl, water, saturated $NaHCO_3$ solution and brine. The organic solution was dried ($MgSO_4$) and evaporated to give the title compound as colorless oil (26g, 85% yield). ^1H NMR: 300MHz spectrum consistent with proposed structure.

Step 9: Preparation of α-methylenebenzenepropanoic acid

The ethyl α-methylenebenzenepropanoate of Step 8 (4.6g, 24.3mmol) was dissolved in methanol (12mL) and then reacted with 2N potassium hydroxide (24mL) solution. The mixture was stirred at room temperature for 4 hours and concentrated by evaporation. The residue was diluted with water and washed with ether. The aqueous layer was acidified to pH 2 with 1N HCl, and then extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and evaporated to give the title compound as colorless oil (2.8g, 66% yield). ^1H NMR: 300MHz spectrum consistent with proposed structure.

Step 10: Preparation of phenylmethyl α-methylenebenzenepropanoate

The title acid of Step 9 (5.2g, 30mmol) was dissolved in dimethylformamide (25mL) and cooled to 0^oC. To this solution potassium carbonate (5.7g, 41.48mmol) was added followed by benzyl bromide (5.7g, 29.7mmol). The mixture was stirred at room temperature overnight. The mixture was filtered and the filtrate was diluted with ethyl acetate, washed with 3 times of water, brine. The solution was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromotography on silica gel, eluting with 90:10 heptane:ethyl acetate to give the pure title compound as colorless oil (4.5g, 60% yield). ^1H NMR: 300MHz spectrum consistent with proposed structure. Anal: calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.69; H, 6.47.

Step 11: Preparation of phenylmethyl α-[[[2-(dimethylamino)ethyl]thio]methyl]benzene-propanoate

The title compound of Step 10 (1.5g, 5.95mmol) was dissolved under argon in methanol (22mL). To this solution was added 2-dimethylaminoethanethiol hydrochloride (843mg, 5.95mmol), piperidine (0.78mL, 7.85mmol) and benzyltrimethylammonium hydroxide (0.25mL, 0.6mmol), and

the mixture was stirred at room temperature for 16 hours. The solvent was removed on a rotary evaporator and then the residue was purified by flash chromotography on silica gel, eluting with 20:1 CH_2Cl_2:MeOH to give the pure title compound (0.5g, 24% yield). ^1H NMR: 300MHz spectrum consistent with proposed structure. Anal: calcd. for $C_{21}H_{27}NO_2S + 0.2H_2O$: C, 69.85; H, 7.65; N, 3.88. Found: C, 69.58; H, 7.60; N, 3.98.

Step 12: Preparation of phenylmethyl α-[[[2-(dimethylamino)ethyl]sulfonyl]methyl]benzene-propanoate

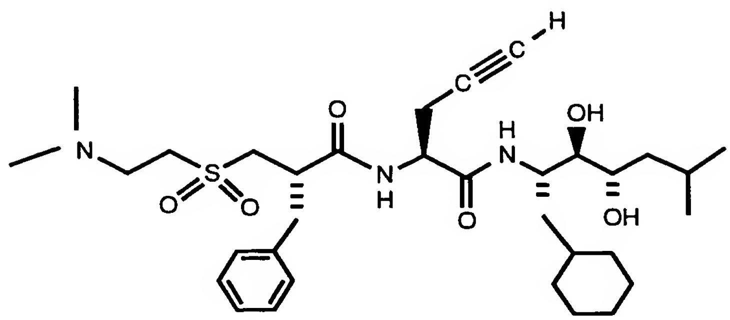
The title compound in Step 11 (0.5g, 1.4mmol) was dissolved in methanol (7mL) and, while cooling with ice, potassium peroxomonosulfate (1.3g) in water (6mL) was added and the mixture was stirred at room temperature overnight. The solution was diluted with water and extracted with methylene chloride, and the extracts were dried (Na_2SO_4) and concentrated by evaporation. The residue was purified by flash chromatography on silica gel, eluting with 20:1 CH_2Cl_2-MeOH to give pure title compound as white powder (400mg, 73%). ^1H NMR: 300MHz spectrum consistent with proposed structure. Anal: calcd. for $C_{21}H_{27}NO_4S$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.01; H, 6.88; N, 3.41.

Step 13: Preparation of α-[[[2-(dimethylamino)ethyl]sulfonyl]methyl]benzeneprop-anoic acid

The title compound of Step 12 (150mg, 0.4mmol) was debenzylated in ethanol with 5psi H_2 at room temperature for 1.5 hours using 4% Pd/C catalyst. After filtering, the solvent was stripped off to give the title compound as white powder (110mg, 70%yield). ^1H NMR: 300MHz spectrum consistent with proposed structure. Anal. calcd. for $C_{14}H_{21}NO_4S$: C, 56.16; H, 7.07; N, 4.68. Found: C, 55.88; H, 6.99; N, 4.35.

The following working Examples are provided to illustrate synthesis of Compounds 1-13 of the present invention and are not intended to limit the scope thereof. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare the compounds of the Examples. All temperatures expressed are in degrees Centigrade.

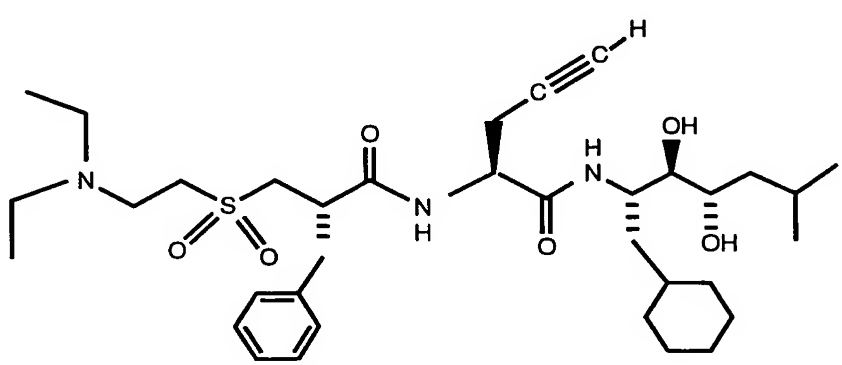
Example 1



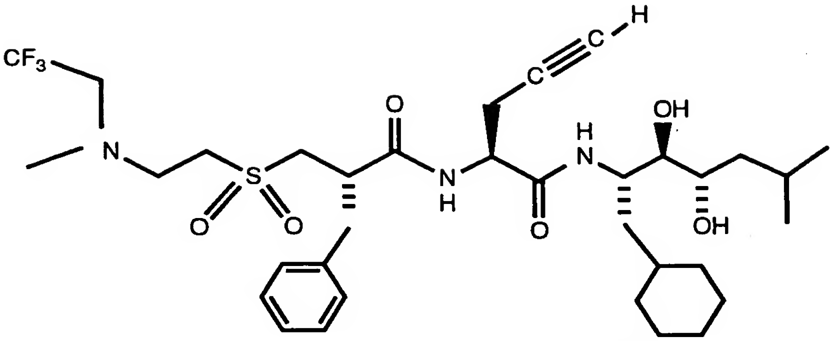
N-[1R*-[[[1S,1R*-(cyclohexylmethyl)-2S*,3R*-dihydroxy-5-methylhexyl]amino]carbonyl]-3-butynyl]-αR*-[[[2-(dimethylamino)ethyl]sulfonyl]methyl]benzenepropana-mide

The title acid of Step 13 is mixed with dry dimethylformamide and stirred at room temperature. To this is added solid N,N'-disuccinimidyl carbonate, followed by pyridine, and finally a solution of dimethylaminopyridine in dimethylformamide. Four hours later, the title amine of Step 7 is added as a solid. The mixture is stirred for 2 days at room temperature. The solvent is then evaporated and the residue taken up in ethyl acetate, washing this layer four times with 5% aqueous potassium carbonate. The organic layer is dried and evaporated to a pale yellow foam. This foam is chromatographed on silica gel, eluting with 10% methanol in methylene chloride containing 1% ammonium hydroxide, to give the pure title compound.

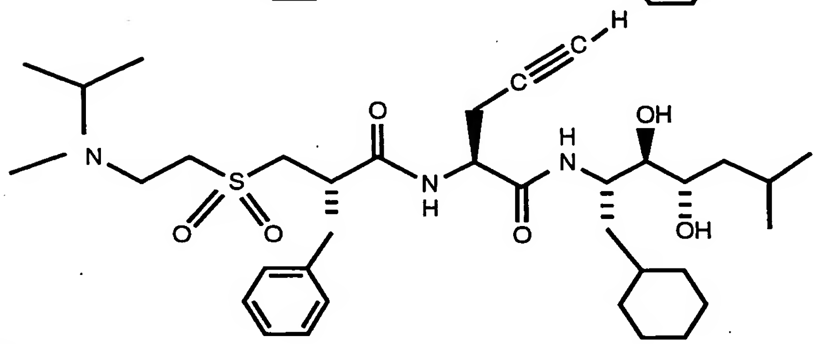
Ex. 2



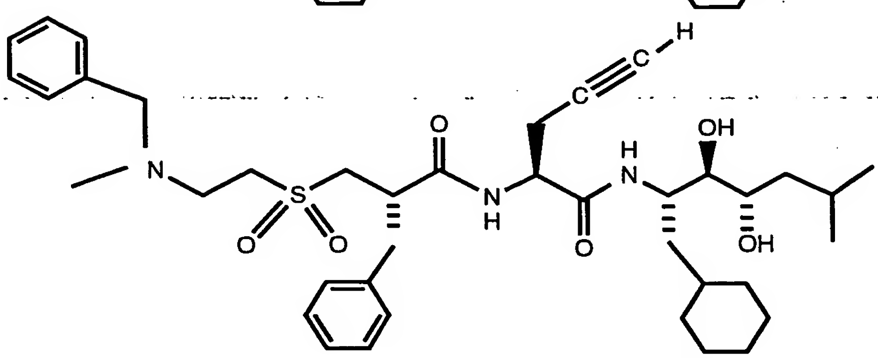
Ex. 3



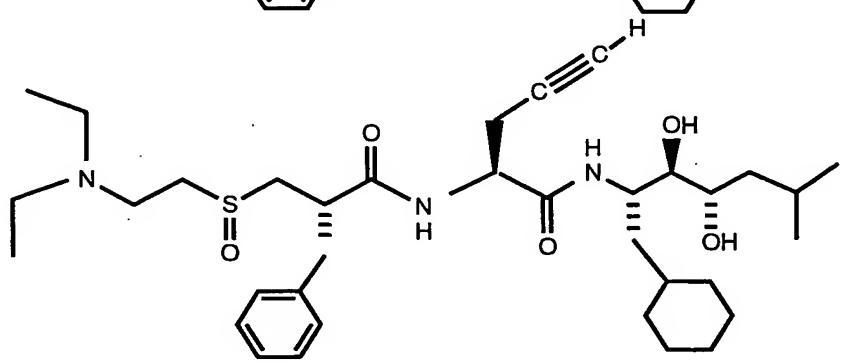
Ex. 4



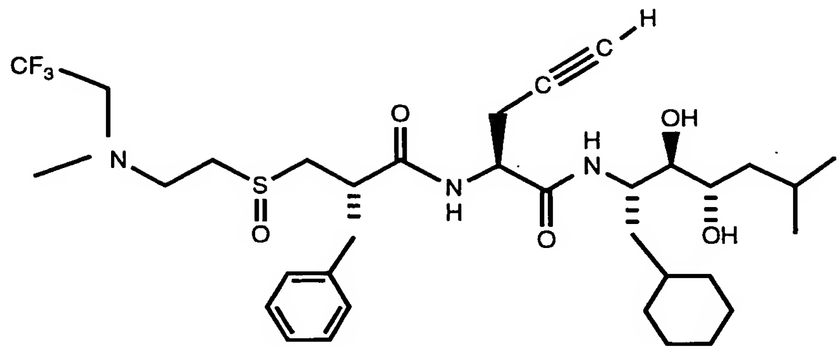
Ex. 5



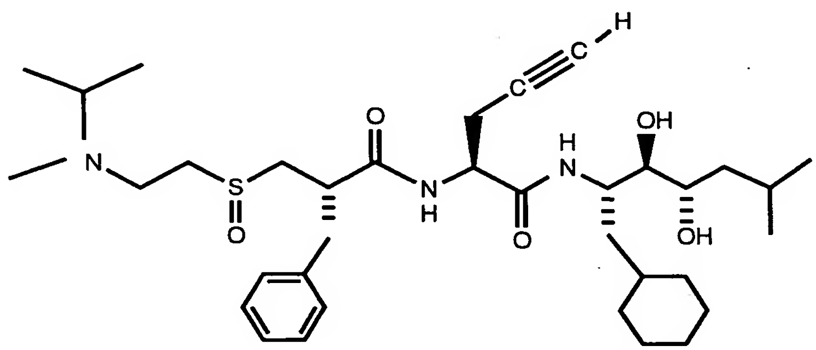
Ex. 6



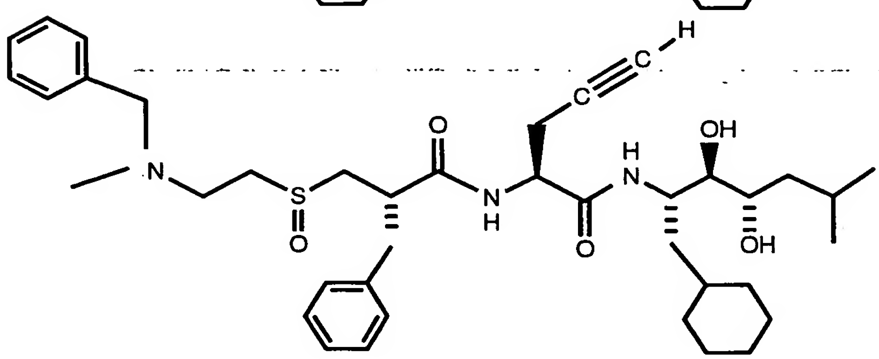
Ex. 7



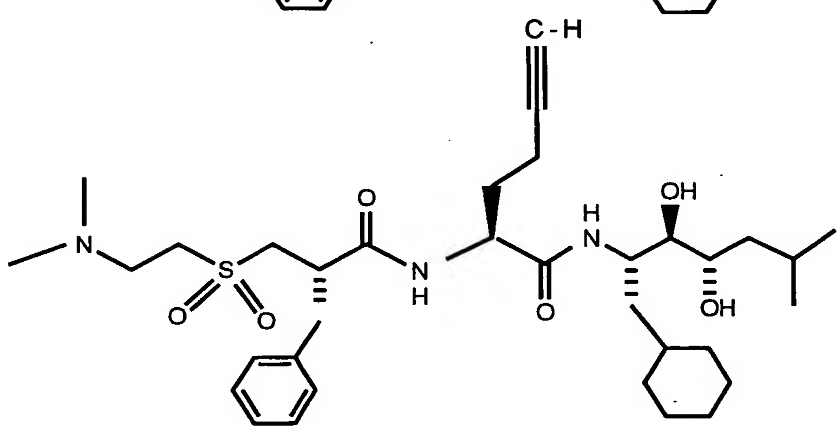
Ex. 8



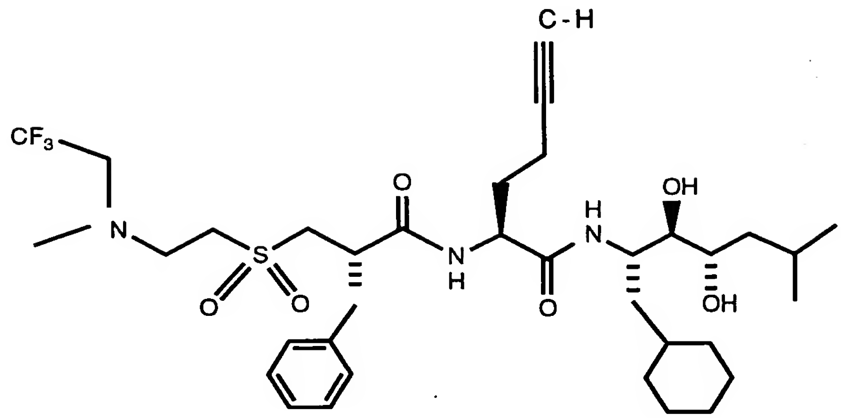
Ex. 9



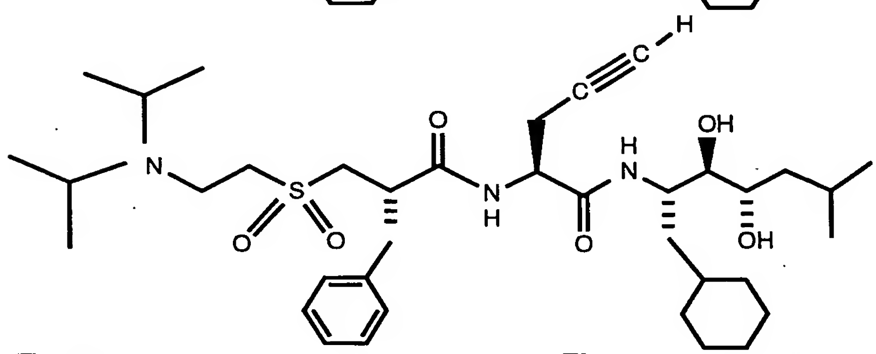
Ex. 10



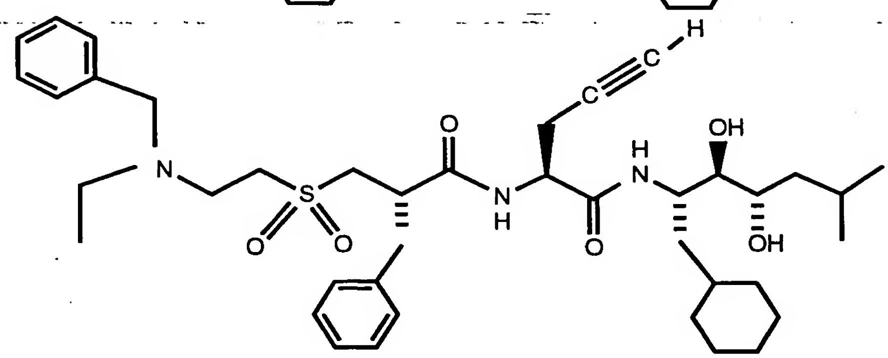
Ex. 11



Ex. 12



Ex. 13



BIOLOGICAL EVALUATION

Human Renin Inhibition *in vitro*

Compounds of Formula I may be evaluated as inhibitors of human renin in an *in vitro* assay, as follows: This human renin inhibition test has been previously described in detail [Papaioannou et al., *Clinical and Experimental Hypertension*, A7(9), 1243-1257 (1985)]. Human renin is obtained from the National Institute for Biological Standards, London. An incubation mixture is prepared containing the following components: in a total volume of 0.25mL: 100 mM Tris-acetate buffer at pH 7.4, 25 x 10^{-6} Goldblatt units of renin, 0.05mL of plasma from human volunteers taking oral contraceptives, 6.0 mM Na-EDTA, 2.4 mM phenylmethyl sulfonyl fluoride, 1.5 mM 8-hydroxyquinoline, 0.4 mg/mL bovine serum albumin (BSA), and 0.024 mg/mL neomycin sulfate. This mixture is incubated for two hours at 37°C in the presence or absence of renin inhibitors. The produced angiotensin I is determined by radioimmunoassay (New England Nuclear kit). Test compounds to be assayed are dissolved in DMSO and diluted with 100mM Tris-acetate buffer at pH 7.4 containing 0.5% BSA to the appropriate concentration. The final concentration of organic solvent in the reaction mixture is less than 1%. Control incubations at 37°C are used to correct for effects of organic solvent on renin activity. The *in vitro* enzymatic conversion of angiotensinogen to angiotensin I would be expected to be inhibited by test compound of the invention.

Also embraced within this invention is a class of pharmaceutical compositions comprising one or more compounds of Formula I in association with one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of the compounds of the present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art. The compounds and composition may, for example, be administered intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of active ingredient from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.1 to 3000 mg/kg body weight, particularly from about 1 to 100 mg/kg body weight, may be appropriate.

The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose is from about 0.1 to 100 mg/kg body weight injected per day in multiple doses depending on the

disease being treated. A preferred daily dose would be from about 1 to 30 mg/kg body weight. Compounds indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 100 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 100 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 50 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 400 mg of active compound per unit dosage form. A more preferred dosage will contain from about 2 mg to about 200 mg of active compound per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 100 mg of active compound per unit dose.

The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular compound employed, and thus may vary widely.

For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered <u>per os</u>, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may

contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.